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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/757,233 | 01/13/2004 | David H. Persing | 014058-017650US | 3248 |

20350 7590 10/05/2006

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| EXAMINER | |
|---|---|
| KHARE, DEVESH | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1623 | |

DATE MAILED: 10/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/757,233 | PERSING ET AL. | |
| | Examiner | Art Unit | |
| | Devesh Khare | 1623 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) 1-35 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-35 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 01/13/2004.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

This application is a continuation of U.S. application Serial Number 09/991,376 filed 11/20/2001 now abandoned.

An action on the merits of claims 1-35 is contained herein below.

**Specification**

(1) The disclosure is objected to because of the following informalities:

The status of the related application cited at the first page of the specification should be updated to ensure a properly completed file record. This application lacks the necessary reference to the issued U.S. Patent No. 6,800,613 which was issued to the parent application serial no. 09/861,466 filed 05/18/2001 which claims benefit of 60/281,567 filed 04/04/2001 and claims benefit of 60/205,820 filed 05/19/2000.

(2) The notation "[]" in the term "MPL[]" (for e.g. See page 2, lines 26 and 27) in all occurrences should be deleted.

Appropriate correction is required.

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double

patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1,2 and 8-13 rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 6,699,846 ('846).

Claim 1 rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 25 of U.S. Patent No. 6,303,347 ('347).

Claim 1 rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 22 of U.S. Patent No. 6,113,918 ('918).

Claims 1 and 6 rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 15 of U.S. Patent No. 7,030,094 ('094).

Claim 1 rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 13 of U.S. Patent No. 7,063,967 ('967).

Although the conflicting claims are not identical, they are not patentably distinct from each other. In each case, the issued patent claims a method comprising administration of a set of compounds wherein said compounds are encompassed by or has substantial overlap with the compounds of the instant method. All the methods are drawn to methods of treating disease or enhancing immune response. It is noted that, as applicant admits, TLRs are known to be important in the immune response (see specification pages 8 and 9) and the production of cytokines (specification page 8,

[0037]). However, the instant method is a method of modulating the production of cytokines in a subject, which is the underlying mechanism by which the methods of the issued claims are accomplished. It would have been obvious to one having ordinary skill in this art, at the time the claimed invention was made to select any of the compounds set forth in the claims of the issued patents and administer them for the claimed method. In doing so, the present method would be achieved.

The examiner notes the instant claims and the '846; '347; '918; '094 and '967 patents of applicants do indeed substantially overlap therefore this obviousness-type double patenting rejection is necessary to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees.
Therefore the claims are co-extensive.

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Claim 1 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 43 of co-pending Application No. 10/137,730.

Claim 1 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim s 91 and 94 of co-pending Application No. 10/068,171.

Although the conflicting claims are not identical, they are not patentably distinct from each other. The co-pending applications claim a method comprising administration of a set of compounds wherein said compounds are encompassed by or has substantial overlap with the compounds of the instant method. All the methods are drawn to methods of treating disease or enhancing immune response. It is noted that, as applicant admits, TLRs are known to be important in the immune response (see specification pages 8 and 9) and the production of cytokines (specification page 8, [0037]). However, the instant method is a method of modulating the production of cytokines in a subject, which is the underlying mechanism by which the methods of the issued claims are accomplished. It would have been obvious to one having ordinary skill in this art, at the time the claimed invention was made to select any of the compounds set forth in the claims of the issued patents and administer them for the claimed method. In doing so, the present method would be achieved.

The examiner notes the instant claims and said co-pending applications of applicants do indeed substantially overlap therefore this obviousness-type double patenting rejection is necessary to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees.

These are provisional obviousness-type double patenting rejections because the conflicting claims have not in fact been patented.

***35 U.S.C. 112, first paragraph rejection***

The factors regarding undue experimentation have been summarized in *In re Wands,* ***Claims* 1-35** are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification, while being enabling for positively modulating (activating) TLR4, does not reasonably provide enablement for the positive and negative modulation of the full scope of TLRs. It is noted that, as applicant admits, TLRs are known to be important in the immune response (see specification pages 8 and 9) and the production of cytokines (specification page 8, [0037]). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

A conclusion of lack of enablement means that, based on the evidence regarding each of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

The factors regarding undue experimentation have been summarized in *In re Wands,* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

(1) The quantity of experimentation necessary (time and expense);

(2) The amount of direction or guidance presented;

(3) The presence or absence of working examples of the invention;

(4) The nature of the invention;

(5) The state of the prior art;

(6) The predictability or unpredictability of the art;

(7) The breadth of the claims; and

(8) The relative skill of those in the art.

1. QUANTITY OF EXPERIMENTATION

With regard to factor one the quantity of experimentation needed, for modulating the production of cytokines in a subject an effective amount of one or more compounds having the formula shown in claim 1, applicant intends to utilize the modulation of cytokines in a subject, would require undue experimentation. At the very least, experimentation correlative to establishing the broad spectrum of efficacy should be provided. The absence of specific disclosures or the correlation of data to support applicant's assertions, invites the skilled artisan to engage in undue experimentation.

2. GUIDANCE PROVIDED

There is little guidance given in the specification as to the specific use of an effective amount of one or more compounds having the formula shown in claim 1 in a subject for modulating the production of cytokines. This lack of guidance would indeed impose the burden of undue experimentation in determining the degree, if any, for the modulating the production of cytokines in a subject set forth. There is not seen any guidance in the specification drawn to establishing a correlation between the use of an effective amount

of one or more compounds having the formula shown in claim 1 in a subject and modulating the production of cytokines.

3. WORKING EXAMPLES IN SPECIFICATION

The examples 1-9 disclose the protection against P. carinii infection; protection against lethal influenza; clinical symptoms and comparison of mouse cultures. The EXAMPLES advanced in the instant specification are not seen as sufficient to support the breadth of the claims for use of an effective amount of one or more compounds having the formula shown in claim 1 in a subject and modulating the production of cytokines.

4. NATURE OF THE INVENTION

In the instant invention is drawn to modulating the production of cytokines in a subject an effective amount of one or more compounds having the formula shown in claim 1, The present specification provides a considerable amount of experimental data. However, the data appear to support only positive modulation (activation) of TLR4. This is bolstered by applicant's publication wherein Baldridge et al (J. Endotoxin Res., 2002) discloses that two of the compounds embraced by the formula recited in claim, RC-524 and RC-529, induce an immunostimulatory response by their ability to activate TLR4. See page 456, 2nd and 3rd full paragraphs.

5. STATE OF THE PRIOR ART; THE PREDICTABILITY OF THE ART; BREATH OF THE CLAIMS and THE RELATIVE SKILL IN THE ART

In the specification the importance of direct binding of LPS to Tlr2 and Tlr4 has been described. However, the data appear to support only positive modulation (activation) of Tlr4.

The role of Tlrs in immunomodulation is reviewed by Quesniaux et al. (Exp. Opin. Ther. Pat.,2004), and it is noted that very few of the references cited therein pre-date the present invention. Therefore, the field related to the modulation of these receptors for modulating the production of cytokines in a subject, is an art that is not well developed, and as such, relatively unpredictable. The reference does provide an overview of the known TLR ligands and their specificity for particular Tlrs (see Table 1). Because of the known specificity of these receptors, it would appear unlikely that the present compounds would interact with any of the TLRs, other than TLR4, to provide any sort of modulation. However, although some specific TLR ligands are known, it is not clear that one of ordinary skill would be able to predict if analogous compounds would work as agonists or antagonists.

The use of TLR inhibitors is known and discussed in Quesniaux et al. (see, for example, section 4.5). Furthermore, as discussed above, the data presented in the specification support only activation of TLR4. The specification provides no guidance for the use of these compounds for modulating the production of cytokines in a subject.

In view of the forgoing, one of ordinary skill would incur a great burden of time and expense necessitated by the undue experimentation required to use this method commensurate with the scope of the claims.

***35 U.S.C. 112, second paragraph rejection***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> *The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.*

***Claim* 23** is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 23 depends from claim 22, which recites the definition of the variable "Y" to be the moiety depicted by the structure fragment. However, claim 23 recites "Y is O..." thus rendering the claim vague and indefinite.

Claims 1-7, 11-16, 18-23 and 25-35 are rejected under 35 U.S.C. 102(e) as being anticipated by Johnson et al (US 6,355,257).

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Johnson et al. ('257) discloses the compounds used in the present invention and the administration of said compounds, exemplifying intranasal administration and administration in an aqueous composition comprising a surfactant, as adjuvants and immunoeffectors. See abstract; col 1-2; test examples; and reference claim 1. Johnson et al also discloses that said compounds stimulate the production of cytokines (col.3, lines 39-41). See discussion of inherent TLR modulation set forth above.

With regard to claim 3, the reference is silent on the use of prodrugs, per se. However, the reference allows for many variations within set of compounds. For example, "$R_8$" can be phosphono or hydrogen. These variations would be considered prodrugs of each other.

Claims 1-5, 11-16, 18-23 and 25-35 are rejected under 35 U.S.C. 102(e) as being anticipated by Johnson et al (US 6,113,918).

Johnson et al. ('918) discloses the compounds used in the present invention and the administration of said compounds, exemplifying intranasal administration and administration in an aqueous composition comprising a surfactant, as adjuvants and immunoeffectors. See abstract; col 1-2; test examples; and reference claim 1. Johnson et al also discloses that said compounds stimulate the production of cytokines (col.3, lines 39-41). See discussion of inherent TLR modulation and prodrugs set forth above.

**35 U.S.C. 103(a) rejection**

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject*

*matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

***Claims* 1-5 and 8-21** are rejected under 35 U.S.C. 103(a) as being unpatentable over Myers et al. (Myers) (U.S. patent 4,912,094).

Myers teaches a genus of 3-O-deacylated lipid A derivatives. See col. 9-10. These compounds have utility as immunostimulants. The reference specifically teaches their use in vaccines comprising a surfactant, such as Tween80. The reference is silent with regard to the modulation of Toll-like receptors, *per sel.* However, as applicant admits, TLRs are known to be important in the immune response (see specification pages 8 and 9) which is responsible for the production of cytokines (specification page 8, [0037]).

It would have been obvious to one having ordinary skill in the art at the time the invention was made to administer the instant compounds as immunostimulants for modulating the production of cytokines. It would be within the scope of the artisan to

determine an effective amount of the compound to achieve immunostimulation. In doing so, the present method would also be achieved.

The fact that applicant has recognized the underlying mechanism for the immunostimulation cannot be the basis for patentability when the differences would otherwise be obvious. The patient population taught by the reference is the same as that of the instant claims. Therefore, the present method of cytokine modulation would naturally flow from using the compounds as taught in the reference.

The reference is silent regarding prodrugs and salts. Prodrugs have been discussed above. In this case, the genus allows for variable phosphorylation. These compounds would be considered prodrugs of each other. It would be obvious to use salts for increased solubility. Neither does the reference specifically suggest any particular method of administering the compounds. It would be within the scope of the artisan to select any common method of administration, such as intranasal, with a reasonable expectation of success.

A skilled artisan would be motivated to make routine modifications to produce instant compounds for pharmaceutical delivery for modulating the production of cytokines because said compounds are immunoeffector molecules.

***Claims* 1-5 and 8-35** are rejected under 35 U.S.C. 103(a) as being unpatentable over Johnson et al. (Johnson) (U.S. patent 6,113,918).

Johnson teaches as set forth above. The reference does not teach $C_2$-$C_6$ acyls at positions "$R^1$", "$R^2$" and "$R^5$". The reference teaches $C_7$-$C_{16}$ acyls at these positions.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare compounds having a $C_6$ acyl at any of these positions. Going from a $C_7$ acyl to a $C_6$ acyl, structures differeing by a single methylene group, would involve the preparation of obvious homologs of the compounds that are exemplified in the reference. In the absence of unexpected results, these homologs would be expected to have the immunostimulating properties thus the capability of modulating cytokines as those disclosed in the reference. It would be further obvious to determine an effective amount, as discussed above.

The fact that applicant has recognized the underlying mechanism for the immunostimulation cannot be the basis for patentability when the differences would otherwise be obvious. The patient population taught by the reference is the same as that of the instant claims. Therefore, the present method of cytokine modulation would naturally flow from using the compounds as taught in the reference.

A skilled artisan would be motivated to make routine modifications to produce instant compounds for pharmaceutical delivery for modulating the production of cytokines because said compounds are immunoeffector molecules.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Devesh Khare whose telephone number is (571)272-0653. The examiner can normally be reached on Monday to Friday from 8:00 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anna Jiang, Supervisory Patent Examiner, Art Unit 1623 can be reached at (571)272-0627. The official fax phone numbers for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status

information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Devesh Khare, Ph.D.,J.D.
Art Unit 1623
September 28, 2006